REMARKS

Claims 1, 5, 6, 9, and 16-34 are pending in this application.

Claims 2-4, 7-8, and 10-15 have been cancelled. Claims 1, 5, 6, and 9 have been amended in this Response. Claims 16-34 have been added.

Introduction.

The present invention is directed to method for detecting the physiological condition of an organism by measuring all low-molecular weight peptides directly detectable by mass spectrometry in a sample from the organism. The physiological condition can be a pathological condition (i.e. related to a disease or syndrome) such as a pathogenic condition (e.g., caused by a bacterium, virus or fungus) or genetic defect. Alternatively, the physiological condition can be related to changes manifested in an organism due to genetic engineering. In preferred aspects of the invention, the physiological condition of the organism is detected without reference to a predetermined or preconceived diagnostic hypothesis. In some preferred aspects, the sample of the organism is prepared for analysis by filtration and/or chromatography prior to measuring the low-molecular weight peptides.

Amended Claims 1, 5, 6, and 9.

Claim 1 has been grammatically amended to more clearly describe that all detectable low-molecular weight peptides by MALDI MS are directly measured in the sample by the defined method for detecting a pathogenic condition. Support for these amendments can be found in the specification, e.g., on page 5, third paragraph, and page 2, last paragraph.

Claim 5 has been grammatically amended to make it consistent with the changes in claim 1 and thereby renders moot the objection to claim 5 on the basis of improper dependency.

Claim 6 has been grammatically amended to more clearly describe that the sample also contains high molecular weight peptides. Support for this amendment can be found, e.g., on page 2, last paragraph.

Claim 9 has been grammatically amended to more clearly describe that the peptides in the fractions are measured under different detection conditions. Support for this amendment can be found, e.g., on page 4, second paragraph and on page 7, third paragraph.

No new matter is added by any of these amendments.

New Claims 16-34.

Claim 16 and claims 17-27 which depend therefrom, are directed to methods for detecting the physiological condition of an organism (e.g., a pathological condition, a pathogenic condition, or physiological changes resulting from genetic engineering) *without recourse to a preconceived diagnostic hypothesis*. Support for these new claims can be found in the original claims of the application, and in the specification at page 1, second paragraph; in the paragraph spanning pages 1 and 2; page 4, second full paragraph and paragraph spanning pages 4 and 5; and at page 5, third paragraph relating to human and veterinary medicine applications of the invention.

Claim 28 and claims 29-34 depending therefrom are specifically directed to detection of pathological conditions (i.e. related to a disease state) *without recourse to a preconceived diagnostic hypothesis*. The method of claim 28 is similar to that of claim 16, with the added step of comparing the differential peptide display of the test organism with the peptide display from an organism having a known pathological condition (i.e., a known disease) in order to diagnose the pathological condition of the organism. Support for these claims is found in the original claims of the application, and in the specification at page 1, second paragraph, in the paragraph spanning pages 1 and 2, and at page 5, third paragraph, and in the paragraph spanning pages 7 and 8.

No new matter is added by claims 16-34.

Claims 1, 5, 6, and 9 Meet all Requirements of 35 USC §112.

Claims 1, 5, 6, and 9 stand rejected for lack of enablement. This rejection is unwarranted, particularly in light of the present amendments to the claims. Each of claims 1, 5, 6, and 9, as now presented of record, is directed to a method for detecting a pathogenic condition (i.e., a disease condition caused by a pathogenic organism such as a bacterial, viral or fungal infection). Any pathogenic condition that results in a change in the low-molecular weight peptide distribution within the organism of interest can be detected by the present method. The specification does not state, and the claimed method does not require that all pathogenic conditions be detectable, only that a pathogenic condition be detectable. The present

specification provides ample description of how to practice the claimed methods. As the Office Action correctly pointed out (on page 2, numbered paragraph 3) the specification is enabling for detecting a pathogenic condition causing a change in peptides having a molecular weight less than 30,000 Daltons. Accordingly, this ground for rejection is unwarranted and should be withdrawn.

Claims 1, 5, 6, and 9 also stand rejected for indefiniteness. This rejection is unwarranted as well to the claims as now presented of record. In claim 1, the phrase "wherein all low-molecular weight peptides present in the sample which can be detected" has been deleted. Thus, the claim has been grammatically amended to more clearly point out that all low-molecular weight peptides having a molecular weight of not more than 30,000 Daltons that are detectable by MALDI mass spectrometry are measured in the sample. There is no ambiguity as to what peptides are measured in the sample. One of ordinary skill in the art of mass spectrometry is well acquainted with the detection limits of MALDI MS and will understand the scope of the claimed method.

The Office Action, on page 3, also states that the description in the specification requires that a separation (e.g., chromatography) step be included in the method prior to measuring the low-molecular weight peptides. That is not the case. Chromatography is not required to practice the method of claim 1. No such requirement is described in the specification. The Examples set forth preferred embodiments of the present invention. It is improper to read limitations from the preferred embodiments into the claims.

Although it is preferable to remove higher molecular weight proteins from the sample, or to fractionate the sample, it is not necessary to do so. The mass spectrometry technique will still be able to detect the various peptides in the sample, regardless of whether there was a separation or not. The relative intensity of the various detected ions of differing mass will provide an indication of the distribution of the various peptides in the sample. Mass peaks having a molecular weight of greater than 30,000 Da can simply be ignored in the data analysis. Furthermore, filtration and chromatography are simply expedients relating to sample preparation. It is recognized that "cleaner" samples will facilitate data analysis somewhat and reduce the frequency of cleaning of the sample inlet port on the mass spectrometer, and thus are some of the

reasons why filtration and chromatography are *preferred.* The method, however, is fully operable without such sample separation steps. The Office Action does not point to any references that indicate that the claimed method would be inoperable without filtration or chromatography. Accordingly, this ground for rejection is unwarranted and should be withdrawn.

None of the Present Claims are Anticipated or Rendered Obvious by the Applied Art.

Claims 14 and 15 were rejected as being anticipated by Tellerova, Shibata, Mabuchi, Leber, Klosse, Nagase, Kodama, or Charpentier. Since these claims have been cancelled, these grounds for rejection are moot.

Furthermore, none of the foregoing cited references teaches all of the limitations of new claims 16-34. In particular, all of the above cited references are directed to detecting for specific peptides in tissue or fluid samples from organisms already having a known disease and associated therewith. In contrast, Claims 16-34 are all directed to methods for detecting the physiological or pathological condition of an organism without reference to a preconceived diagnostic hypothesis (i.e., not knowing the disease of the organism, if any). None of the cited references takes this approach. In fact, the International Preliminary Examination Report specifically found this feature to be the point of novelty and inventiveness for the present invention (See the International Preliminary Examination Report for PCT/EP97/04396, pages 3-5, explanations 3 and 4). Claims 16-34 have refocused the invention on this novel and inventive feature.

Claims 1, 5, 6, and 9 were rejected as being obvious over Tellerova, Shibata, Nagase, Mabuchi, Leber, Kodama, Klosse, or Charpentier in view of Jimenez or Wang. This rejection is unwarranted and should be withdrawn. Amended claims 1, 5, 6, and 9, as now presented of record, are all directed to methods for detection of *pathogenic* conditions (i.e., conditions caused by a bacterium, virus or fungus). Only the Leber reference is even marginally related to pathogenic conditions.

Leber is directed to the use of chromatographic methods to detect middle-molecular weight peptides in a serum ultrafiltrate from patients suffering from hepatic coma, which can be caused by hepatitis. Leber does not teach or suggest a method for detecting a pathogenic disease

by directly measuring all low-molecular weight peptides detectable by MALDI mass spectrometry in a sample from an organism and comparing the distribution of the detected peptides in the sample with a reference distribution.

Neither do Jimenez or Wang, taken singly or in combination, cure the defects of Leber or the other primary references in relation to the presently claimed invention. Jimenez merely demonstrates that MALDI MS can be used to detect neuropeptides from a single neuron and suggests the use of the technique for studying the synthesis and expression of bioactive peptides (see the Abstract).

The combination of Leber and Jimenez does not teach or suggest all of the limitations of claims 1, 5, 6, or 9 as presented of record. The combination of these references does not teach or suggest a method for detecting a pathogenic condition in an organism wherein the distribution of low-molecular weight peptides in a sample from an organism is determined by measuring all MALDI MS detectable low-molecular weight peptides having a molecular weight of not more than 30,000 Da.

Leber detects the presence of peptides by thin layer chromatography (TLC). There is nothing in Leber to suggest that the TLC detection technique is inadequate for the purpose for which it is being used or to suggest a need to consider other techniques. Jimenez teaches that known neuropeptides can be detected and identified using MALDI MS. Jimenez focuses on the advantages of using the MS technique to measure the expression of known neuropeptides by comparison of the mass peaks from the MS experiment to the known masses of the neuropeptides. When the identity of the peptides are unknown, there is little advantage evident in using mass spectrometry from the teachings of Jimenez, since the mass of a peptide, alone, provides little guidance for identifying an unknown peptide substance. There is no teaching in either reference that would have motivated one of ordinary skill in the art to attempt to detect all MS detectable low molecular weight peptides in a sample by MALDI MS as required by claims 1, 5, 6, and 9 for purposes of detecting a pathogenic condition in an organism.

The combination of Leber and Wang also fails to teach or suggest all of the limitations of claims 1, 5, 6, or 9 as presented of record. Wang focuses on measurement of the presence and amount of a known protein (soluble β amyloid protein) by MALDI MS. The combination of

Leber and Wang does not teach or suggest detecting all MALDI MS detectable low-molecular weight peptides in a sample from an organism by MALDI MS. Like Jimenez, Wang is directed to detecting the presence of known peptides or proteins in a sample. This is unlike the indiscriminate detection of all detectable low-molecular weight peptides, as practiced in the present invention. There is nothing in Leber that suggests a need for or desirability of using a detection method other than simple thin layer chromatography

The combination of Tellerova, Shibata, Nagase, Mabuchi, Kodama, Klosse, or Charpentier with either Jimenez or Wang is even further removed from the presently claimed methods than the combination of Leber with Jimenez or Wang. Tellerova, Shibata, Nagase, Mabuchi, Kodama, Klosse, Charpentier, Jimenez and Wang all focus on the identification of known peptides. None of these references individually teaches or suggests a method for detecting a pathogenic condition in an organism, nor can any combination of these references provide such a teaching.

Accordingly, claims 1, 5, 6, and 9 as presented are not obvious over any combination of Tellerova, Shibata, Nagase, Mabuchi, Leber, Kodama, Klosse, or Charpentier in view of Jimenez or Wang. Allowance of claims 1, 5, 6 and 9, as presented of record, is warranted.

With regard to new claims 16-34, as discussed earlier and repeated here by reference, these claims are all directed to a method of detecting the physiological or pathological condition of an organism without regard to a preconceived diagnostic hypothesis. Unlike the present invention, all of the above cited references involve measuring for specific peptides in a sample from an organism having an already known disease or condition. No combination of these references teaches or suggests a method for detecting the condition of an organism without first knowing (i.e., having a preconceived hypothesis of) what diseased condition the organism suffers from. Accordingly, none of claims 16-34 is rendered obvious by any combination of the applied references.

Conclusion.

Applicants submit that all of the presently pending claims 1, 5, 6, 9 and 16-34 are in condition for allowance. Early allowance of all claims is earnestly solicited.

Respectfully submitted,

Dated: January 8, 2004

By: Dolores T. Kenney
Dolores T. Kenney (Reg. No. 31,269)

OLSON & HIERL, LTD.
20 North Wacker Drive
36th floor
Chicago, Illinois 60606
(312) 580-1180

CERTIFICATE OF MAILING

I hereby certify that this correspondence and fees referred to therein are being deposited with the United States Postal Service as first class mail with sufficient postage in an envelope addressed to: Commissioner for Patents, P. O. Box 1450, Alexandria, Virginia 22313-1450, on January 8, 2004.

Dolores T. Kenney
Dolores T. Kenney